amendments contain no new matter. Support for the amendments to the claims may be found in the specification.

The Examiner rejected claims 35, 37 and 40 under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101.

In response, applicants have amended claims 35, 37, and 40, thus rendering the Examiner's rejection moot. Accordingly, applicants request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. 101.

In the Office Action, the Examiner rejected claims 15, 17,and 31-40 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention.

In response, Applicants have amended claim 15, thus rendering the Examiner's rejection moot. Accordingly, claims 17 and 31-40 are in compliance with the requirement under 35 U.S.C. 112, second paragraph.

In addition, claim 30 has been amended in compliance with the Examiner's objection.

Applicants respectfully maintain that the claims are definite and particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 112.

In the Office Action, the Examiner rejected claims 15-40 under 35 U.S.C. §103(a) as being unpatentable over Bodor, U.S. Patent No. 4,824,850 and Naito, JP 05339148 A2 (abstract).

Applicants hereby traverse the Examiner's rejection of the claims under 35 U.S.C. 103. Applicants maintain that none of the references either alone or in combination renders obvious Applicants' invention.

The Examiner asserted that Bodor teaches the use of pyridinium derivatives and associated salts for the delivery of pharmaceuticals through the blood brain barrier (BBB). The Examiner further asserted that Naito teaches the use of sugars to allow pharmaceuticals to pass through the blood brain barrier. The Examiner alleged that it would have been obvious to modify the teachings of Bodor in view of Naito to obtain the claimed invention.

Contrary to the Examiner's assertions, the Examiner has not raised a prima facie case of obviousness in the case of the Bodor reference.

Bodor uses neutral reduced compounds to enter the brain, which comprise a substituted dihydropyridine moiety. According to Bodor, the dihydropyridine moiety is not a drug but rather functions as a carrier moiety for a pro-drug type compound.

According to Bodor, the dihyropyridine moiety, being neutral, is permeable to the BBB, while the corresponding quaternary pyridinium derivatives are impermeable. For example, Bodor specifically teaches "that it is clear that it is the most difficult for quarternary pyridinium or ammonium salt to penetrate the BBB" (Col. 2, lines 58-60).

In contrast to the compounds of Bodor, the compounds of the present invention are novel derivatives of the drug pyridostigmine, a compound which is considered in the art to be impermeable to the BBB. The compounds of the present invention are hydrophobic BBB permeable derivatives of pyridostigmine, and as such comprise the pharmacologically active portion of the drug.

The dihydropyridine carrier moiety and derivatives thereof of Bodor are exclusively substituted with carboxyl groups at the 3-position, through which the so-called active drug moiety is attached either directly or through a spacer/linker group. Thus, these compounds are not derivatives of pyridostigmine, and are not referred to as such in the Bodor refeence.

In contrast to the compounds of Bodor, the compounds of the present invention are derivatives of pyridostigmine, which is a positively charged pyridinium carbamate drug comprising a quaternary amine at the ring nitrogen and carbamoyl group at the C-3 position of the ring. This carbamoyl group is known to be

a crucial element of the physiological activity of the drug pyridostigmine. Unmodified, pyridostigmine is impermeable to the BBB. The present invention provides pyridostigmine derivatives modified through substitutions on the ring nitrogen which render the drug derivatives permeable to the BBB despite the positive charge of the molecule. These substitutions to the ring nitrogen-comprising lipophilic alkyl chains terminating with a sugar or modified sugar group - are radically different from the compounds disclosed by Bodor, which, in addition to not being derivatives of pyridostigmine, have a different set of proposed substitutions on the ring nitrogen, both for the case of the BBB permeable compounds (e.g. dihydropyridine derivatives) and for the BBB impermeable compounds (e.g. pyridinium salt derivatives).

According to the Bodor reference, the pyridinium compounds are specifically described therein to be impermeable to the BBB. In fact, this impermeability is described as being a crucial feature of the Bodor invention, wherein the dihydropyridine derivatives are presumed to undergo oxidation only after entering a cell to yield a corresponding pyridinium derivative which then, being impermeable, remains within the cell. Thus, in fact, Bodor teaches away from the modification of charged pyridinium derivatives to obtain permeable compounds, other than through chemical reduction in the preparation of the corresponding dihydropyridine for administration as a carrier moiety. Again,

the pyridinium derivatives of Bodor are not derivatives of pyridostigmine, and indeed are not considered to be drugs at all but rather are either synthetic precursors or metabolized products of the dihydropyridine moieties proposed by Bodor as carrier groups for drugs.

In contract to the compounds of Bodor, the compounds of the present invention are derivatives of the drug pyridostigmine, modified to be permeable to the BBB. The only similarity between the Bodor compounds and those of the present invention is in that both comprise a pyridinium ring structure. While the positively charged quaternary pyridinium compounds of Bodor are impermeable, the present invention provides modified pyridostigmine derivatives which are permeable to the BBB, despite their positive charge. In addition to the difference substitutions at the C-3 position, i.e., carbamoyl, the charged pyridinium ring derivatives of Bodor and those of the present invention differ with respect to the substitutions at the ring nitrogen, those of Bodor having a different set of ring N-substitutions, none of which comprises a sugar attached through a hydrocarbyl group spacer.

According to Bodor, the permeability-enhancing moiety of his invention is an uncharged dihydropyridine derivative carrier group, whereas the BBB permeable compound of the present invention is a charged quaternary pyridinium moiety rendered

permeable through the addition of lipophilic alkyl chains comprising a terminal sugar group.

The Examiner asserted that Bodor teaches the conjunction (indirectly or directly) of substituted pyridinium salts with sugars or poly substituted nontoxic polyols (Col. 44, lines 50-68).

In response, the Applicant respectfully points out that the Examiner's assertion is incorrect with respect to the present invention. Bodor proposes a particular modification to a trigonelline--dihydrotrigonelline delivery system that is unrelated to any one of the compounds of the present invention, with the exception of the presence of a pyridinium ring. The modification proposed by Bodor (Col. 44 therein) is conjunction of a mono- or poly-substituted nontoxic polyol (such as inositol or sugars ) at the C-3 carboxyl group for the purpose of linking a drug moiety to the carrier moiety. Bodor neither discloses nor suggests that the use of such a linker group would improve the permeability of the resultant compound, but rather merely teaches that the use of polyols may be a convenient spacer/linker group between the drug and the carrier moieties of his invention at the C-3 position. In any case, Bodor's compounds are not pyridostigmine derivatives. Thus Bodor's teachings are irrelevant to the present invention.

In contrast, the present invention teaches the conjunction of sugar and related groups at the ring nitrogen position using a hydrocarbyl spacer group for the purpose of obtaining pyridostigmine derivatives which are BBB permeable.

In regard to the Naito reference, the Examiner asserted that this reference discloses a substance that contains certain sugars in combination with certain amino acids and obtains a substance that at least partially penetrates the BBB. Applicants respectfully point out that this reference refers to a sugar-amino acid combination and on these grounds alone is irrelevant to any aspect of the present invention.

Furthermore, as is well known in the art, the addition of a sugar group is more likely than not to reduce, rather than to enhance, the permeability of a compound to a biological barrier. While it is known in the art that the attachment of certain sugar groups, and derivatives thereof, may serve to enhance the bioavailability of a compound, the effect of such an addition is a function of a multitude of factors including, *inter alia*, the particular parent compound, the particular sugar, the point of attachment, and the type of spacer group employed. Thus, as for the case of the present invention, the determination of a particular set of molecular configurations in which the attachment of a sugar group to a drug derivative provides the benefit of enhanced permeability for that derivative is a matter

of extensive experimentation. Were the opposite to be true, then virtually every drug, whether intended for CNS delivery or otherwise, would be provided with one or more sugar groups, which of course is not the current state of the art by any stretch of the imagination.

Thus, the Examiner has not provided any basis to support a rejection of the claimed invention. Moreover, even if one would combine the references, the references would not teach or disclose Applicants' invention. Specifically, by combining the above-cited references, one of ordinary skill in the art would not obtain any one of the compounds of the present invention, but rather at best, compounds which comprise sugar-amino acid group additions which are just as likely to be of reduced rather than enhanced bioavailability. Since none of the references cited discloses sugar groups attached through a hydrocarbyl spacer, there is no motivation to combine the references. Evident as well is that no possible combination of the references could lead to pyridinium derivatives comprising a ring nitrogen having a sugar group attached through a hydrocarbyl spacer. It is foremost evident that no possible combination of the references could lead to derivatives of pyridostigmine.

Therefore, the above-cited references do not render obvious Applicants' invention. Accordingly, Applicants respectfully

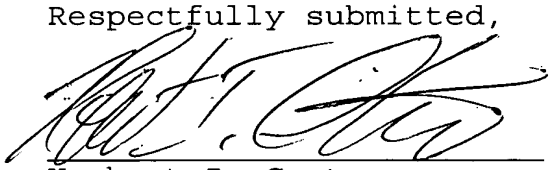
request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. 103.

Based on the foregoing, Applicants request allowance of the claims. Applicants believe that they have addressed all issues raised by the Examiner and that the claims as amended are in condition for allowance, which is earnestly requested. Should the Examiner have any questions or comments as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #3103/44139).

Respectfully submitted,

November 22, 2000



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